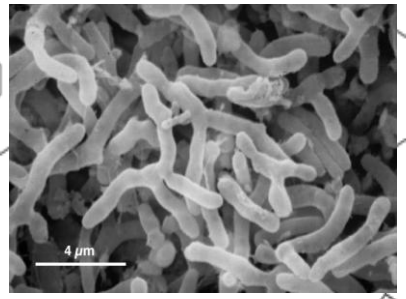
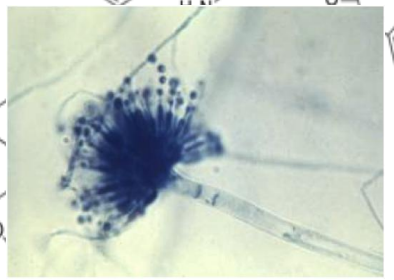
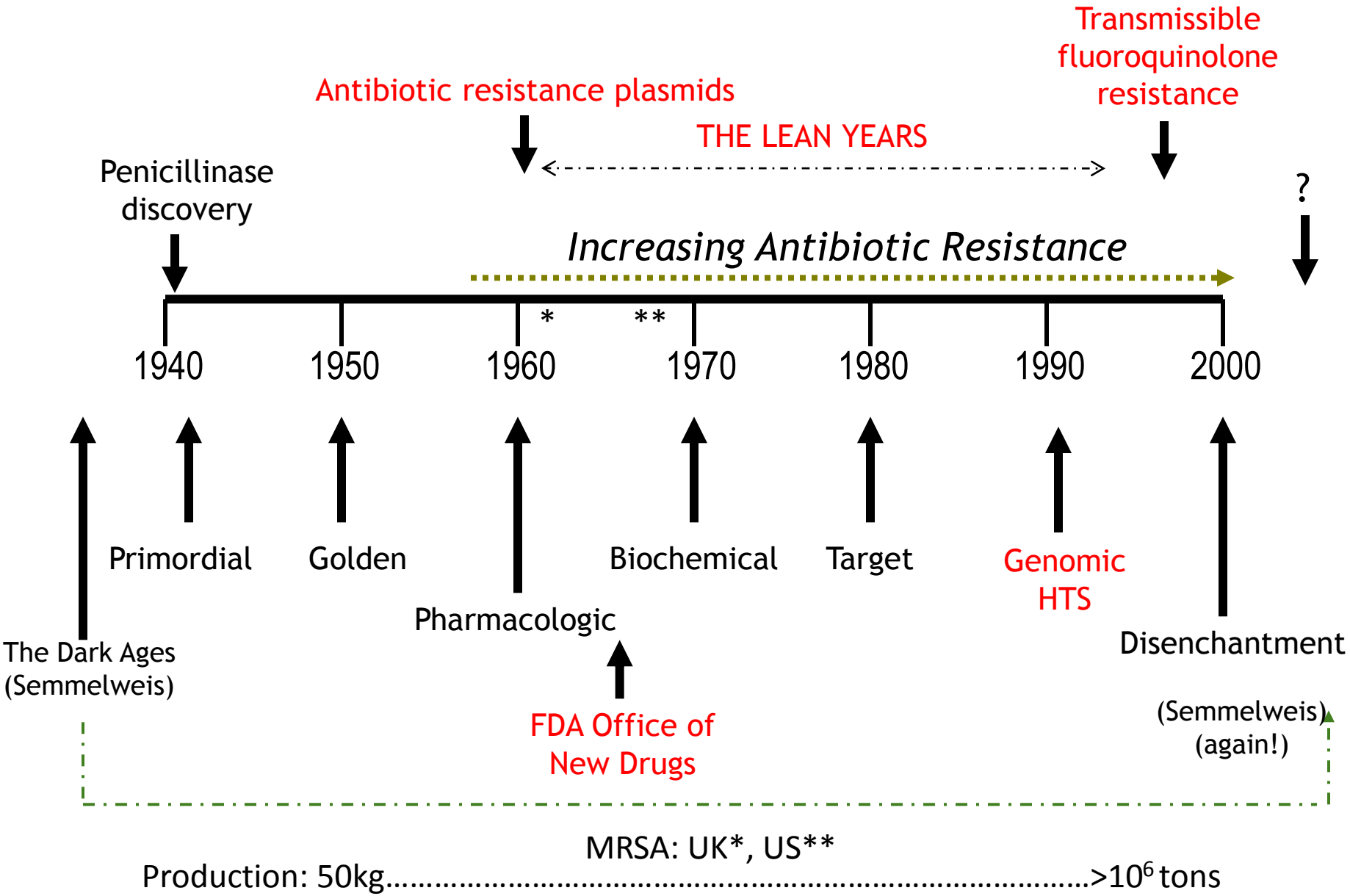
New approaches to address antibiotic resistance in animals





ATA, Paris, 25/09/2012

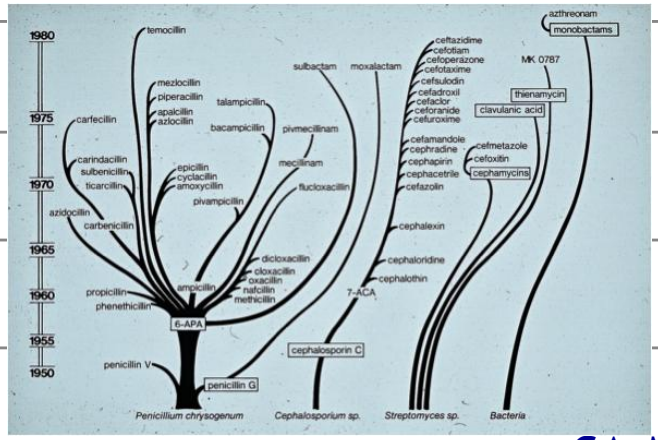
The co-evolution of antibiotics and their resistance



MRSA: UK*, US**

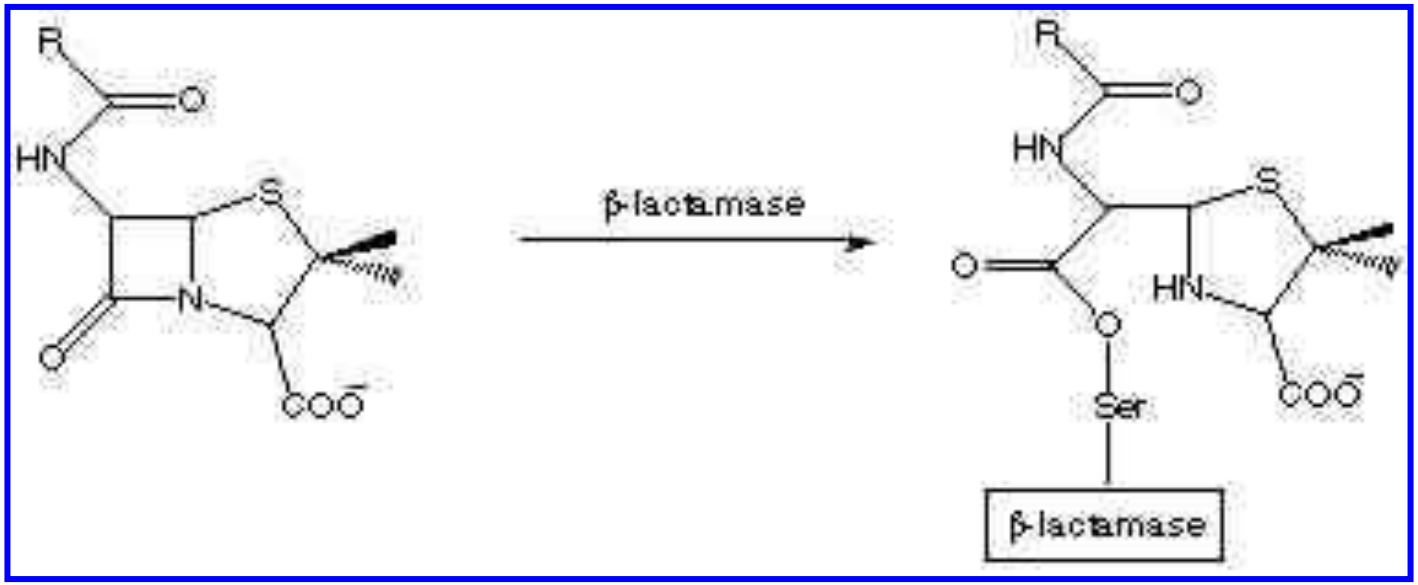
Production: 50kg……>10^6 tons

Evolution of ß-lactamases
FIFTY YEARS OF MRSA!



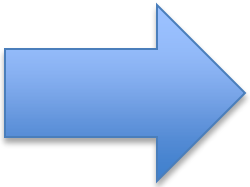
Information provided by Karen Bush

The most expensive hydrolytic reaction in history!



Fifty years of “Industrial Research” on Antibiotics

Environmental
Doubling time: months
Aeration: low
Nutrients: variable
Carbohydrate: limited
Water: variable
Temperature: 0-40
pH: 2-10
Yield: µgrams



Production
Doubling time: hours
Aeration: high
*Nutrients: high and constant
Carbohydrate: high
Water: unlimited
Temperature: 25-30
pH: 6-7
Yield: grams

***Typical substrates for fermentation**
Molasses (blackstrap)
Fish Meal (herring, anchovy)
Citrus pulp
Asparagus juice
Cottonseed oil
Malt extract
Beef extract
Bovine blood
Pork liver
Distillers solubles
Hydrolysed rabbit fur

We Live In A Microbial World

Microbial viruses on the Earth: $1x10^{31}$

Microbes on the Earth: $5x10^{30}$

Stars in the Universe: $7x10^{21}$

Humans on the Earth: $6x10^{9}$

Human genes in one person: $2.5x10^{4}$

Human cells in one person: $1x10^{13}$

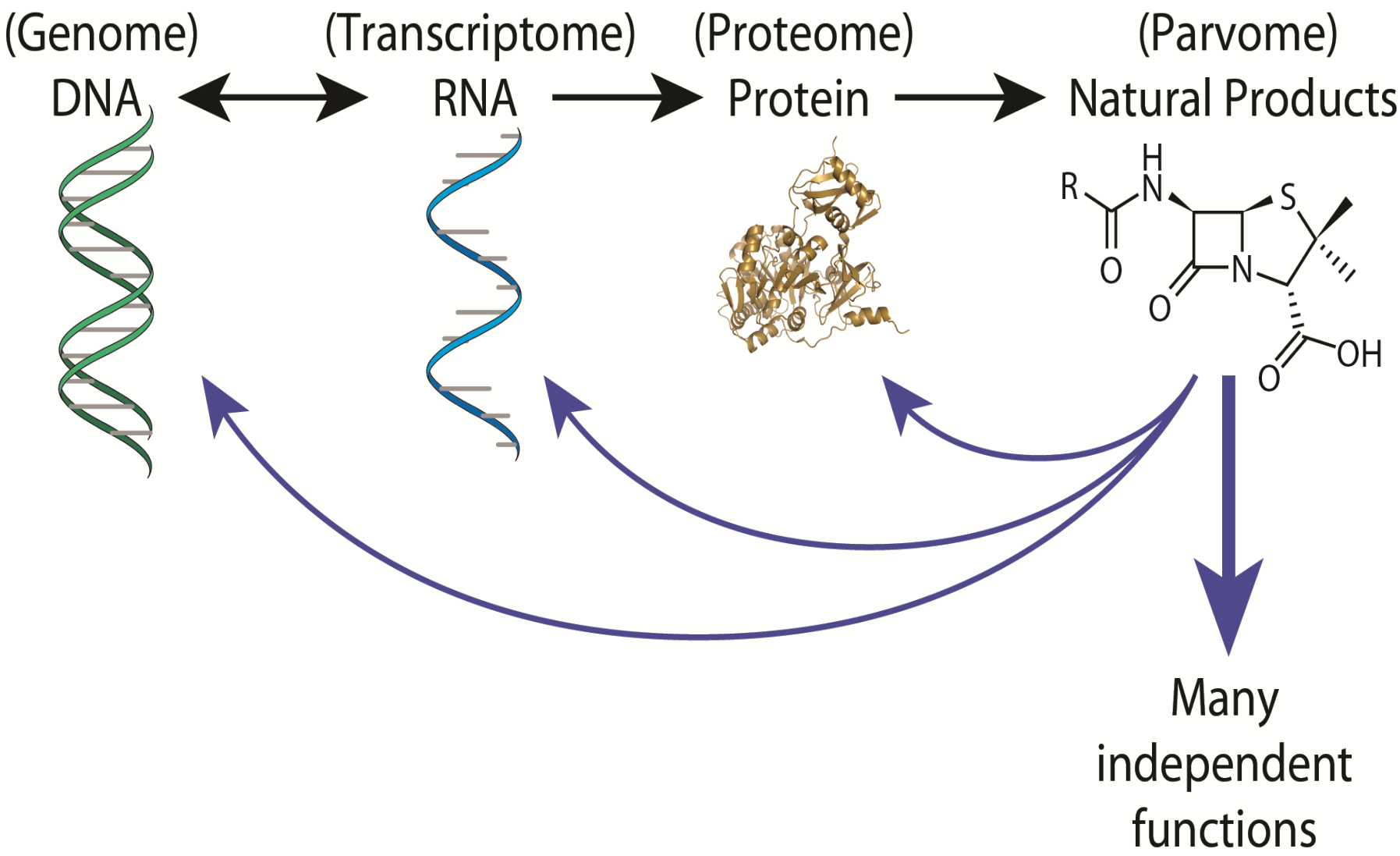
Microbial genes in human gut: $3x10^{6}$

Microbial cells in human gut: $1x10^{14}$

Bubbles in one bottle of champagne: $1x10^{5}$

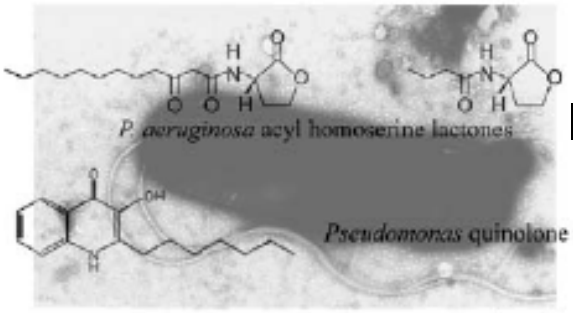
We are less than 10% of what we think we are!

The "Revised" Central Dogma



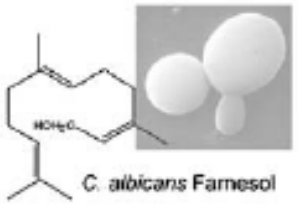
"Life would not exist with macromolecules alone." Stuart Schreiber, 2005

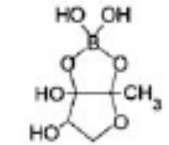
MONERA

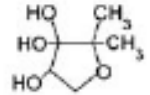


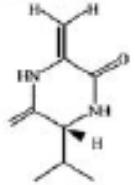
Inter-Kingdom Signalling

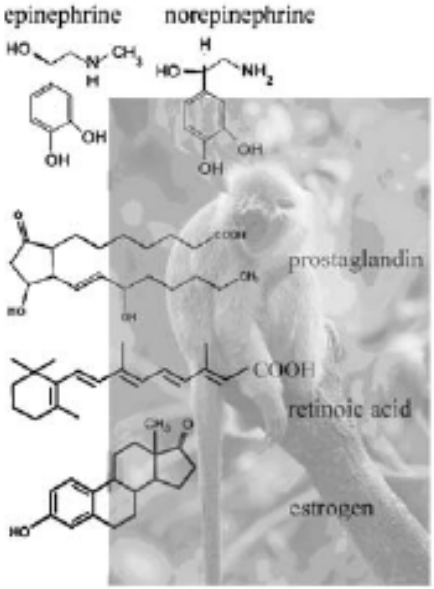
FUNGI



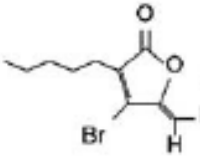




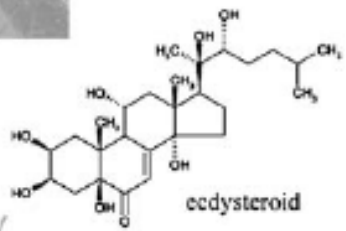


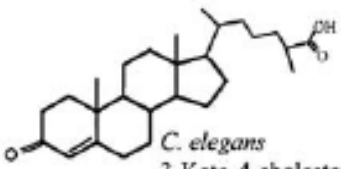


The Parvome

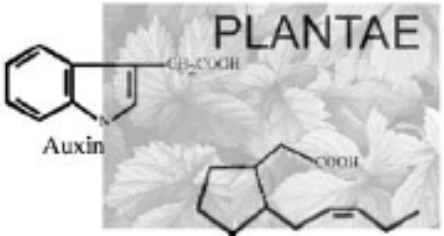


ANIMALIA



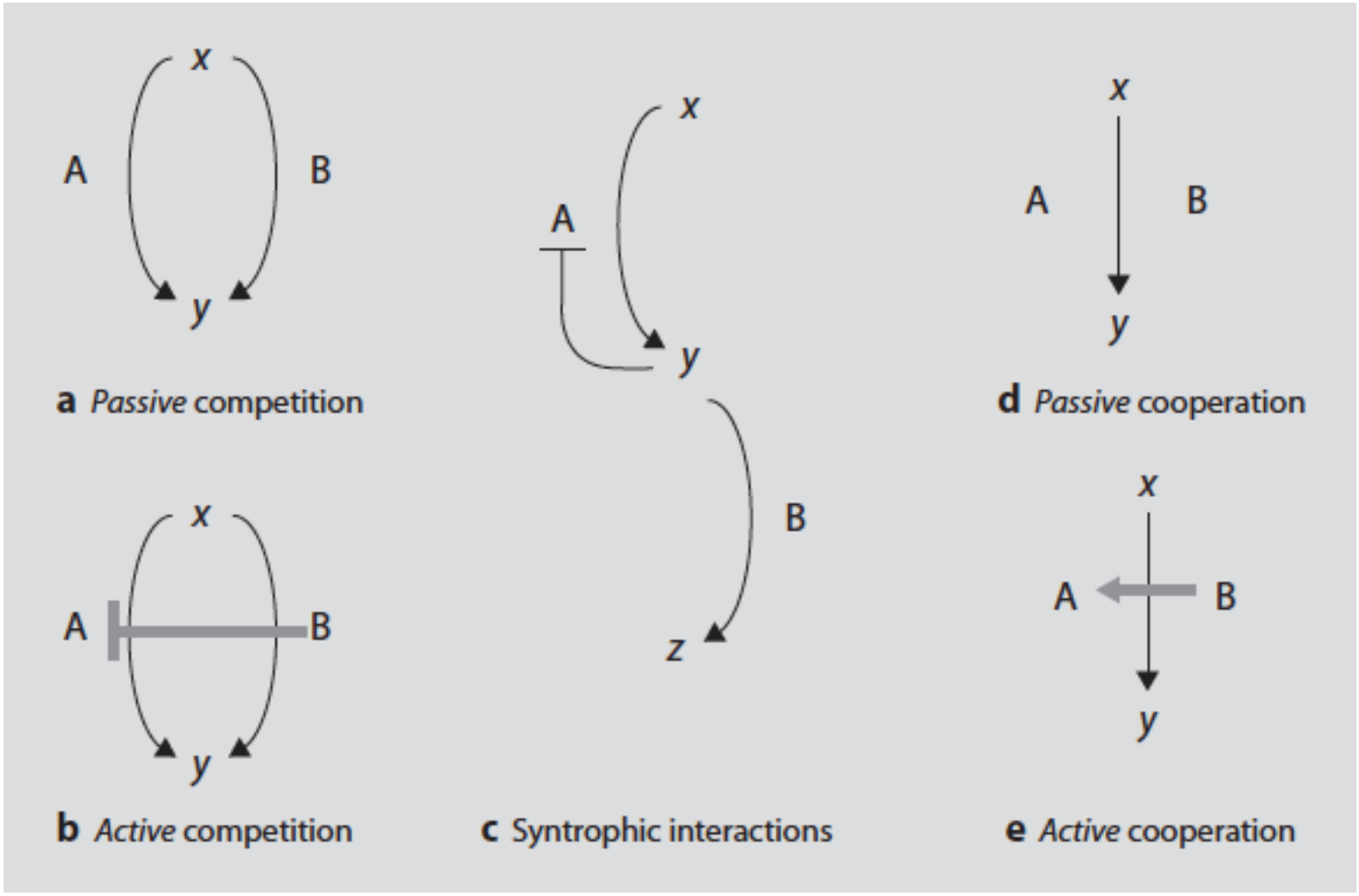


PLANTAE



(Rumbaugh, 2007)

Signaling Interactions between Cells in Nature
(Communication, Cues, Competition, Cooperation)



Duan et al, 2009

Prospects for natural product drug discovery

- Bioactivity-based screens
- Combinatorial synthesis and biosynthesis
- Chemical library screening by “docking”
- Co-culturing producing strains: pathway activation
- Genomic identification of biosynthetic pathways
- Heterologous expression of pathways
- Drug combinations
- New approaches to vaccines
- A “new” look at plants and other sources
- Personalized treatments

Genomics and Drug Discovery

(A new paradigm)

Genome or Metagenome sequence

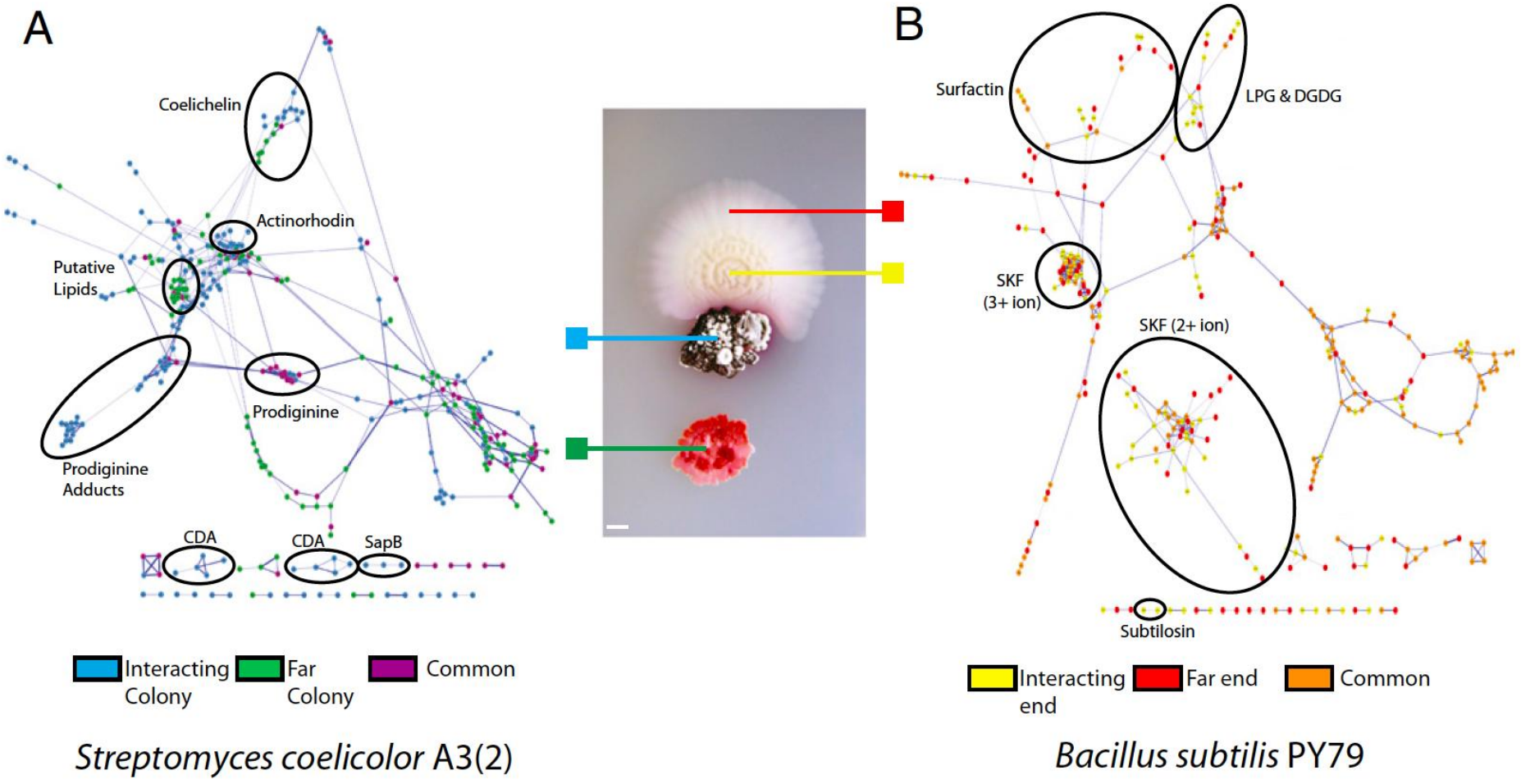
Bioinformatic scanning for biosynthetic gene clusters

Prediction of structure or molecule class

Virtual docking for target identification

Compound production by
cluster expression
in “designer” host

Analysis of molecular interactions in bacterial cell networks, using high-resolution MS with nanoDesi probe (Watrous *et al* 2012)




THE OTHER OPTION?